DR FLORA PEYVANDI (Orcid ID : 0000-0001-7423-9864)

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Caplacizumab reduces the frequency of major thromboembolic events, exacerbations, and death in patients with acquired thrombotic thrombocytopenic purpura

F. Peyvandi[*], M. Scully[†], J. A. Kremer Hovinga[‡], P. Knöbl[§], S. Cataland[¶], K. De Beuf[**], F. Callewaert[**], H. De Winter[**], R. K. Zeldin[**]

[*] Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Via Pace 9, 20122 Milan, Italy

[†] Department of Haematology, University College London Hospital, 60 Whitfield Street, W1T 4EU London, UK

[‡] University Clinic of Hematology & Central Hematology Laboratory, Inselspital, Bern University Hospital and Department of Clinical Research, University of Bern, Freiburgstrasse 8, 3010 Bern, Switzerland

[§] Medical University of Vienna, Department of Medicine 1, Div. Hematology and Hemostasis, Waehringer Guertel 18-20, 1090 Vienna, Austria

[¶] Department of Internal Medicine, Ohio State University, 410 West 10th Avenue, 43210 Columbus, OH, USA

[**] Ablynx NV, Technologiepark 21, 9052 Zwijnaarde, Belgium

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Corresponding author:

Robert K. Zeldin

Clinical Development, Ablynx NV, Technologiepark 21, 9052 Zwijnaarde, Belgium

Tel +32 92620000

Fax +32 92620002

Email: robert.zeldin@ablynx.com

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Essentials

- Acquired thrombotic thrombocytopenic purpura (aTTP) is linked with significant morbidity.
- Caplacizumab's effect on major thromboembolic (TE) events, exacerbations and death was studied.
- Fewer caplacizumab-treated patients had a major TE event, an exacerbation, or died vs. placebo.
- Caplacizumab has the potential to reduce the acute morbidity and mortality associated with aTTP.

Summary

Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a life-threatening autoimmune thrombotic microangiopathy. In spite of treatment with plasma exchange and immunosuppression, patients remain at risk for thrombotic complications, exacerbations and death. In the Phase II TITAN study, treatment with caplacizumab, an anti-vWF Nanobody®, was shown to reduce the time to confirmed platelet count normalization and exacerbations during treatment.

Objective: The clinical benefit of caplacizumab was further investigated in a post-hoc analysis of the incidence of major thromboembolic events and exacerbations during the study drug treatment period and TTP-related death during the study.

Methods: The Standardized MedDRA Query (SMQ) for 'embolic and thrombotic events' was run to investigate the occurrence of major thromboembolic events and exacerbations in the safety population of the TITAN study, which consisted of 72 patients of whom 35 received caplacizumab and 37 received placebo.

Results: Four events (1 pulmonary embolism and 3 aTTP exacerbations) were reported in 4 patients in the caplacizumab group, while 20 such events were reported in 14 patients in the placebo group (2 acute myocardial infarctions, 1 ischemic and 1 hemorrhagic stroke, 1 pulmonary embolism, 1 deep vein thrombosis, 1 venous thrombosis and 13 aTTP exacerbations). Two of the placebo-treated patients died from aTTP during the study.

Conclusion: In total, 11.4% of caplacizumab-treated patients versus 43.2% of placebo-treated patients experienced one or more major thromboembolic event, an exacerbation or died. This analysis shows the potential for caplacizumab to reduce the risk of major thromboembolic morbidities and mortality associated with aTTP.

Introduction

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening autoimmune blood clotting disorder, manifested by systemic microvascular thrombosis leading to profound thrombocytopenia, hemolytic anemia, and organ ischemia[1]. It is caused by inhibitory autoantibodies to the von Willebrand Factor (vWF)-cleaving protease, ADAMTS13[2]. Decreased ADAMTS13 activity leads to an accumulation of ultra-large (UL) vWF multimers which bind to platelets and induce formation of microthrombi, causing tissue ischemia and organ dysfunction, and may result in overt major thromboembolic complications such as stroke, myocardial infarction, and arterial and venous thrombosis[3, 4]. Episodes of aTTP are associated with an acute mortality of up to 20%[5], with most deaths occurring within 30 days of diagnosis[6] (median of 9 days[3]).

The current mainstay of aTTP treatment is plasma exchange (PE) in conjunction with immunosuppression (e.g., with glucocorticoids and/or rituximab)[7]. PE removes ULvWF and autoantibodies and replenishes ADAMTS13, while immunosuppression inhibits autoantibody formation. However, current treatment has a slow onset of action and does not immediately address the pathophysiological platelet aggregation that leads to the formation of microthrombi[8].

Caplacizumab, an anti-vWF Nanobody®, immediately blocks the interaction of ULvWF with platelets and, therefore, inhibits further formation and accumulation of microthrombi. The efficacy and safety of caplacizumab have been evaluated in the phase II TITAN study[9]. Seventy-five patients with a clinical diagnosis of aTTP were randomized. Although ADAMTS13 activity was not part of the eligibility criteria, 77% of patients had a baseline ADAMTS13 activity <10%, while 11% had ADAMTS13 activity levels of 10% or more, and baseline ADAMTS13 results were missing for the remaining 12%. The results of the study showed that treatment with caplacizumab, as compared to

placebo, resulted in 39% faster normalization of platelet counts[9]. This translated into a reduced need for PE treatment (7.7 days vs. 11.7 days for placebo). Treatment with caplacizumab was also associated with a higher complete remission rate (i.e., confirmed platelet count response and absence of exacerbation) (81% vs. 46% for placebo), fewer exacerbations during the treatment period (3 patients vs. 11 for placebo), and a reduction in the percentage of patients refractory to treatment (5.7% vs. 21.6%, or 0% vs. 10.8% for placebo, depending on the definition used for refractoriness[10]). Seven patients in the caplacizumab group experienced a relapse within ten days after stopping study drug. All had ADAMTS13 levels that remained below 10%, suggesting unresolved autoimmune activity. The main safety finding was increased mild bleeding, mainly mucocutaneous, without requirement for vWF/FVIII administration.

Here we report the results of a post-hoc analysis of the TITAN study data which evaluated the impact of treatment with caplacizumab on the incidence of major thromboembolic events and exacerbations during the study drug treatment and aTTP-related mortality during the study.

Methods

The Phase II TITAN study was a randomized, single-blind, placebo-controlled, multicenter study in adults experiencing an acute episode of aTTP requiring treatment with PE[9]. The main inclusion criteria were a clinical diagnosis of aTTP requiring the initiation of plasma exchange and a platelet count of less 100,000 per cubic millimeter.

Seventy-five patients were randomized in a 1:1 ratio to receive either 10 mg caplacizumab or placebo daily in addition to standard-of-care throughout the PE period and for 30 days after thereafter. The safety population (i.e., all patients who received at least one dose of study drug) consisted of 72 patients, of whom 35 received caplacizumab and 37 received placebo, and was used for this analysis.

Major thromboembolic events were retrieved from the study's safety database (i.e., all adverse events as reported by the Investigators) using the Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ) for 'embolic and thrombotic events'. This query contains pre-determined sets of MedDRA preferred terms for 'arterial', 'venous', and 'vessel type unspecified and mixed arterial and venous' events (MedDRA version 19.1 was used). Medical review of the output resulted in exclusion of two reported treatment-emergent adverse events from the analysis. One event was reported as 'thrombotic catheter', but was an obstruction within the malfunctioning catheter itself and not a venous thrombosis. The second event was reported as 'thrombocytopenia', but was present at baseline. Transient ischemic attacks were not considered major thromboembolic events and were, therefore, also not included in this analysis. 'Thrombotic thrombocytopenic purpura' is a predefined term in the SMQ 'thrombotic and embolic events'. aTTP exacerbations are captured in the SMQ output as they reflect acute worsening of the presenting episode. They are reported as 'aTTP exacerbations'. TTP-related mortality during the study was evaluated based on adverse event reporting, with relatedness to aTTP as judged and reported by the investigator. The number of events and the number and percentage of patients having an event or who died were summarized by treatment group for the safety population. The event times of major thromboembolic events, TTP exacerbations and TTP-related death were presented graphically by treatment group.

Results and Discussion

After medical review of the events defined by the SMQ, a total of 8 major thromboembolic events were identified (Table 1). One major thromboembolic event was reported in 1 patient in the caplacizumab group: 1 pulmonary embolism. In the placebo group, 7 major thromboembolic events were reported in 6 patients: 2 acute myocardial infarctions in 2 patients (reported verbatim terms were 'non S-T elevation myocardial infarction' and 'acute myocardial infarction', respectively), 1

ischemic and 1 hemorrhagic stroke in 1 patient (reported as separate events within the same patient; both events had the same onset and end date), 1 pulmonary embolism, 1 deep vein thrombosis (reported verbatim term was 'right lower extremities deep vein thrombosis'), and 1 venous thrombosis (reported verbatim term was 'gemellar muscular veins thrombosis'). The frequency of major thromboembolic events in the placebo group was consistent with that reported in the literature[3, 4].

The output of the SMQ also reflects the aTTP exacerbations that were reported as serious adverse events during the study drug treatment period. In total, 3 aTTP exacerbations occurred in 3 caplacizumab-treated patients versus 13 aTTP exacerbations in 11 placebo-treated patients (Table 1). TTP exacerbations re-expose patients to the same acute thrombotic risks of the disease. In the French TTP Registry, death was reported in 14% of the patients with an exacerbation[11].

Two patients died during the study, both in the placebo group (Table 1). One patient died from severe refractory TTP, after 22 days of intensified daily plasma exchange treatment and immunosuppressive treatment (i.e., cyclophosphamide and rituximab). The second patient died from a cerebral hemorrhage after 10 days of daily plasma exchange throughout which platelet counts were in the range of $30x10^9$/L. These findings are consistent with published data which show that refractoriness to treatment is an indicator of a poor prognosis for survival in patients with aTTP[12-14]. Of note, caplacizumab has been shown to reduce the incidence of refractoriness to therapy[10].

The composite analysis of major thromboembolic events and aTTP exacerbations during the study drug treatment period and aTTP-related deaths during the study showed that 11.4% of caplacizumab-treated patients versus 43.2% of placebo-treated patients experienced one or more

thromboembolic events, an exacerbation or died, which represents a 74% reduction (Table 1). All reported events occurred in patients with a baseline ADAMTS13 activity <10%, except for 3 events in 3 placebo-treated patients: 1 patient with a myocardial infarction (missing baseline ADAMTS13 result), 1 patient with a fatal cerebral hemorrhage (baseline ADAMTS13 75%) and 1 patient with an exacerbation (baseline ADAMTS13 90%). Of note, if these patients were excluded from the analysis, the results would have still favored caplacizumab.

The time-to-event analysis indicates that the majority of these events occurred within the first 30 days of enrollment (Figure 1). Most of the major thromboembolic events occurred during the daily PE period, while by definition, aTTP exacerbations occurred after reaching an initial platelet response (range: within 7-30 days of enrollment). These data confirm that patients experiencing an aTTP episode are at greatest risk for these life-threatening complications during this acute period.

Major thromboembolic events may contribute to long-term cognitive and physical deficits of patients experiencing an episode of aTTP[15-20]. The impact of treatment with caplacizumab on the frequency of major thromboembolic events and exacerbations in the phase II TITAN study was highly clinically meaningful. By reducing acute thromboembolic complications and exacerbations, treatment with caplacizumab may also improve longer term outcomes. A Phase III study with caplacizumab in patients with aTTP is ongoing (NCT02553317), which will prospectively evaluate these important clinical endpoints as a composite endpoint consisting of major thromboembolic events, exacerbations and aTTP-related death. In addition, patients who completed the Phase III study will be followed in a long term follow-up study (NCT02878603).

Authorship details

F. Peyvandi: designed research, performed research, collected data, analyzed and interpreted data, reviewed manuscript

M. Scully: designed research, performed research, collected data, analyzed and interpreted data, reviewed manuscript

J. A. Kremer Hovinga: designed research, performed research, collected data, analyzed and interpreted data, reviewed manuscript

P. Knöbl: designed research, performed research, collected data, analyzed and interpreted data, reviewed manuscript

S. Cataland: designed research, analyzed and interpreted data, reviewed manuscript

K. De Beuf: designed research, analyzed and interpreted data, performed analysis

F. Callewaert: designed research, analyzed and interpreted data, wrote manuscript

H. De Winter: designed research, analyzed and interpreted data, wrote manuscript

R. K. Zeldin: designed research, analyzed and interpreted data, wrote manuscript

Disclosure

P. Knöbl reports personal fees from Ablynx during the conduct of the study; grants, personal fees from Shire, Novo Nordisk, Alexion, and CSL Behring outside the submitted work.

F. Callewaert has a patent on “Stable formulations of immunoglobulin single variable domains and uses thereof” (PCT/EP2014/060107; NL 1040254) pending.

F. Peyvandi reports grants and personal fees from Ablynx during the conduct of the study; personal

fees from Bayer, Grifols, Novo Nordisk, Sobi, Alexion, Kedrion Biopharma, Freeline, LFB, Octapharma, and F. Hoffmann-La Roche Ltd outside the submitted work.

Other authors have nothing to disclose.

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Tables

Table 1. Treatment-emergent major thromboembolic events and aTTP exacerbations during the treatment period and overall aTTP-related mortality in the Safety Population of the Phase II TITAN study

	Caplacizumab (N=35)			Placebo (N=37)		
	# Events	# Patients	% of Patients	# Events	# Patients	% of Patients
Major thromboembolic events (based on SMQ, by preferred term)						
Acute myocardial infarction[1]	0	0	0	2	2	5.4
Pulmonary embolism	1	1	2.9	1	1	2.7
Deep vein thrombosis[2]	0	0	0	1	1	2.7
Venous thrombosis[3]	0	0	0	1	1	2.7
Ischemic stroke[4]	0	0	0	1	1	2.7
Hemorrhagic stroke[4]	0	0	0	1	1	2.7
aTTP exacerbations (based on SMQ, by preferred term)						
Thrombotic thrombocytopenic purpura[5]	3	3	8.6	13	11	29.7
aTTP-related mortality						
Deaths related to TTP	0	0	0	2	2	5.4
TOTAL	4	4[6]	11.4	22	16[6]	43.2

[1] verbatim terms: one acute myocardial infarction was reported as 'non S-T elevation myocardial infarction', one as 'acute myocardial infarction'

[2] verbatim term: 'right lower extremities deep vein thrombosis'

[3] verbatim term: 'gemellar muscular veins thrombosis'

[4] the ischemic and hemorrhagic stroke were reported as separate events within the same patient. Both events had the same onset and end date

[5] this preferred term consisted of recurrences of aTTP during the treatment period, defined and reported per protocol as exacerbations of TTP

[6] a patient may have experienced more than one event

Figure legend

Figure 1. Event times of major thromboembolic events, TTP exacerbations and TTP-related death by treatment group. Time is expressed as days from first dose of study drug.

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